The Role of Complement in Antibody Therapy for Infectious Diseases

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ABSTRACT The complement system is part of the innate immune system, eliciting central immunoregulatory functions. Detection of foreign surfaces is either achieved through complement-specific pattern-recognition molecules or mediated by antigen recognition of antibodies. Immunoglobulin A (IgA), IgG, and IgM all have the potential to initiate a complement response, with the efficiency and response development closely related to the antibody isotype, multimeric state, and degree of glycosylation. A group of serum proteins constitutes the central effector functions of complement, thus allowing direct cell lysis, opsonization, and inflammation. These effector functions can be used in antibody therapies, especially against infectious diseases, as the target membranes lack complement regulatory proteins. The relative contribution of each function and the interplay with direct antibody-mediated clearance is not fully exploited, thus suggesting an option for further rational optimization of antibody therapies.

INTRODUCTION
The complement system is an integral and evolutionarily ancient component of the innate immune system, serving as the first line of defense against common pathogens (Fig. 1) (1). The prime functions of complement in innate host defense are accomplished through three effector pathways. These include lysis, inflammation, and opsonization (Fig. 2). The latter is central to microbial recognition and clearance by phagocytic cells. Complement further cooperates with Toll-like receptors in response to microbial structure and infection, in which immune responses are determined through both synergistic and antagonistic manners (1). Complement is also a functional bridge between innate and adaptive immunity, orchestrating an integrated host defense response to pathogenic challenges. For instance, complement can modulate adaptive immunity by providing signals that reinforce humoral responses to antigens by priming and regulating T cells and lowering the B-cell activation threshold (2, 3). It is also an important integral point for cross talk with other biological cascades to ensure homeostasis is maintained. One example is the interplay between the complement and coagulation cascades, whereby the complement system can amplify coagulation by enhancing local clotting and, as a result, preventing microbial spread through the systemic circulation. Likewise, the activated clotting factor XII can activate the classical complement pathway and thrombin can directly cleave the third and fifth complement components (C3 and C5, respectively) (4, 5).

In addition to effector functions, complement also plays a vital role in the maintenance of homeostasis by aiding in the removal of cell debris and aging cells from the host in a noninflammatory manner. The safe removal of endogenous debris is tactful, whereby apoptotic cells are opsonized without downstream amplification that
would result in inflammation, thus ensuring cell integrity and maintenance of homeostasis (6). Complement also plays regulatory roles in organ regeneration, neuroprotection, and the mobilization of hematopoietic stem progenitor cells from the bone marrow (6).

On account of its potency, selectivity, and rapid amplifying nature, complement plays a central role in the field of antibody (Ab) therapy. A promising future has been forecast for Abs in the treatment of many pathologies, including cancer and infectious diseases, owing to their targeting properties and efficient use of inherent elimination procedures. However, there are only a few drugs on the market and in clinical trials for the treatment of infectious diseases, mainly due to competition pressure from cheaper broad-spectrum antibiotics (7) and the crucial need for correct early diagnosis. Consequently, Ab therapy is unlikely to outcompete treatments for diseases where cheaper and efficient treatments are widely accessible. Nevertheless, emerging antimicrobial drug resistance affirms the need for more targeted treatments, as in methicillin-resistant Staphylococcus aureus (8), where Ab treatments could have potential.

Anti-infectious Ab therapy targets either the pathogen or its toxins. Currently, there is only one approved anti-infectious monoclonal antibody (MAb) on the market (palivizumab) for the treatment of respiratory syncytial virus infection in infants (9). A further few are currently in clinical trials (7). The highly complex nature of Ab binding in affinity and effector functions is another challenge in the development of new and more-efficient therapeutic Abs. This was the case for motavizumab, an intended new and improved version of palivizumab. However, clinical trials were disappointing both in the lack of efficacy and in initiating adverse reactions in some patients (7).

Abs mediate pathogen elimination through different effector mechanisms (Fig. 2). Surface neutralization is one approach, where bound Abs form a barrier that passivates the invading pathogen independent of Fc isotype (10). Moreover, bound Abs can directly recruit effector cells to the site of interest. This may result in pathogen engulfment via Fc receptors (FcRs), complement receptors (CRs), and/or cytokine release. The latter process is known as Ab-dependent cell cytotoxicity (ADCC) and may involve natural killer cells, macrophages, neutrophils, and eosinophils. Finally, bound Abs recruit the complement components that kill the cell either directly by complement-dependent lysis (complement-dependent cytotoxicity [CDC]) or through C1q and/or C3b/C3b opsonization processes that activate leukocytes (complement-dependent cell cytotoxicity [CDCC]).

The advantage of Ab therapy is in its targeting properties. A preparation of MAbs consisting of a single purified Ab with only one epitope may target specific infectious agents and leave host resident flora cells undisturbed. The response development from Ab binding to pathogen killing or elimination is, however, complex.

FIGURE 1 Schematic representation of complement activation by pathogens. The diagram shows the role of surface-bound antibodies and other complement-sensing molecules in complement triggering. Serum IgA is monomeric, but IgA in secretions is dimeric. IgM is pentameric. P, properdin; AP, alternative pathway.

Accordingly, important considerations on the effector mechanisms must be made to achieve the full potential of the formulation, where complement plays a central role.

**COMPLEMENT ACTIVATION**

The complement system consists of more than 30 circulating and cell-bound proteins (11). This array of proteins is organized into a hierarchy of proteolytic cascades operating through three major distinct pathways: the classical, lectin, and alternative pathways (Fig. 1). These pathways all converge at the step where C3 is cleaved by C3 convertases, thereby amplifying complement response and propagating the cascade.

**Classical Pathway**

The classical pathway is primarily Ab dependent and is initiated by antigen–Ab complexes (4). Only immunoglobulin G (IgG) clusters and IgM are capable of initiating the classical pathway directly (12). C1q has a hexameric structure, which is formed by six globular heads that are held together by a collagen-like tail. Together with two other proteins, C1r and C1s, they form the C1 complex. Upon binding of more than one globular head of the C1q to the constant regions of IgG/IgM or directly to a pathogen surface, C1q undergoes a conformational change that can activate zymogens C1r and C1s, forming an enzymatically active C1 complex that cleaves the C2 and C4 proteins to form the classical pathway C3 convertase, C4b2a.

**Lectin Pathway**

The lectin pathway is triggered when mannose-binding lectin (MBL) and ficolins bind to a surface. These species recognize repeating carbohydrate patterns (e.g., mannose and N-acetylated sugars) on invading pathogens. Host cells also display carbohydrate units, but these are protected by sialic acid, which prevents the binding of MBL (13). The binding of MBL or ficolin to a surface triggers activation of their associated serine protease zymogens (mannose-activating serine protease 1 [MASP-1], MASP-2, and MASP-3). Activated MASP-2 cleaves C4, which in turn results in C2 cleavage and formation of a C3 convertase identical to that of the classical pathway.

**Alternative Pathway**

The alternative pathway is spontaneously activated at a low but constant rate (tick over). This is also a mechanism that provides an ongoing probing of the surrounding cells. There are abundant amounts of circulating C3 in the host, which is spontaneously hydrolyzed to C3bH2O. This exposes a binding site for factor B. Upon binding, factor B is cleaved by factor D, forming the alternative pathway fluid-phase C3 convertase C3bBb. The resulting soluble convertase cleaves C3 to give C3a and C3b. The latter can attach to pathogen or host cells, where covalently bound C3b binds factor B, which in turn is rapidly cleaved by factor D, forming surface-bound C3bBb and aiding deposition of many molecules of C3b on the surface. Properdin, a positive complement regulator, stabilizes the C3bBb convertase, extending its half-life severalfold (14). On host cells, complement regulatory proteins such as CR1 and decay-accelerating factor can displace Bb from...
C3b. Factor H is also recruited and accelerates Bb displacement from C3b. In addition to these processes, CR1, membrane cofactor of proteolysis, and factor H catalyze the cleavage of bound C3b by recruiting the plasma protease factor I to produce inactive C3b.

C3 convertases from all three pathways can cleave C3 into C3b and C3a components, with the deposits of C3b quickly forming new C3 convertases in the presence of factor B and D through the alternative pathway. This positive reinforcement turns into a large amplification loop, responsible for 80 to 90% of complement response, independent of the original pathway (6).

Ab-MEDIATED COMPLEMENT ACTIVATION

The three Ab subtypes, IgA, IgG, and IgM, have shown complement-activating properties (Fig. 1). Collectively, they are able to activate all three complement pathways, with IgG-mediated classical pathway activation standing as the most essential. Common to all isotypes is the requirement of a tight interaction between the Ab and a surface (e.g., a cell membrane, allograft, or drug carrier surface). This binding induces a conformational change in the Fc/Fab hinge regions or associates the Abs into a spatial orientation that allows the complement proteins (e.g., C1q, C3b) to become both bound and activated. The conformational change is vital for complement activation. For example, IgG can bind to some particulate materials (e.g., SiO2 particles), but the binding may not be strong enough to accomplish the conformational change necessary for efficient complement activation (15). IgMs also require specific conformations for activation, as they have been shown to bind equally well on different-sized dextran nanoparticles but only induce complement activation when a distinct curvature criteria is fulfilled (16).

IgG

IgG is the most abundant immunoglobulin isotype and is believed to be the most important in complement activation. It is responsible for the linkage between the diversification of the adaptive system and the rapid response of complement, as IgG can bind to epitopes on nonself surfaces, resulting in recruitment and activation of C1q via the classical pathway. The active conformation of C1q is achieved by the binding of more than one C1q head group to Fcγ domains of surface-bound IgGs. Multiple IgGs must therefore be bound to a surface in a proper intermolecular distance to be able to initiate a complement response.

There are four subtypes of IgG (IgG1 to IgG4), each with different biological activities (C1q and FcR affinity) and pharmacokinetic profiles (half-life and protease susceptibility) (17). IgG1 is the isotype used in the majority of MAbs because of its ability to strongly associate with both C1q and FcγR while possessing good circulation half-lives and stability. IgG3 has a similar biological activity, only with a reduced half-life, which is most likely due to a longer hinge region that renders the Ab susceptible to proteolysis. Despite the lack of biological activity from IgG2 and IgG4, these isotypes have shown superior bactericidal function against *Cryptococcus neoformans* infections in mice (18). This finding highlights the complex effector function in Ab therapies in general and suggests specific demands for different infections. It further questions the general role of complement in Ab therapies and is discussed below.

IgM

Another activator of the classical pathway is the IgM Ab, which possesses an activation mechanism similar to that of IgG. Secreted IgMs circulate in its inactive, planar pentameric conformation. When efficiently bound to a target surface, the pentamer adopts a staple conformation by kinking its Fab regions relative to the Fc plane. This change in conformation exposes binding sites for C1q and initiates a complement response. The fact that a single pentamer is sufficient to initiate complement further removes the requirement for specific Ab densities. Accordingly, IgM species could make promising candidates in MAb therapies, provided that the production of stable expression of the native pentameric form can be achieved on a large scale (19).

IgA

The role of IgA in complement activation is less studied, though IgA can activate complement through different pathways. It activates the lectin pathway mainly by acting as a ligand for MBL (20). Furthermore, it is also believed to increase the alternative pathway turnover (21, 22). Its complement-activating properties largely depend on its multimeric state and its extent of glycosylation, with the most potent activators being the polymeric and heavily glycosylated species. Polymeric IgA is also a ligand for the FcαR present on phagocytes and has thereby shown, in concert with its complement-activating properties, to mediate phagocytosis of *Streptococcus pneumoniae* (21). This elimination mechanism is highly similar to the IgG-mediated activation through FcγR affinity. However, where IgG can induce phagocytosis directly through FcγR in the absence of complement activation, IgA-mediated
killing is dependent on phagocyte preactivation by C5a or tumor necrosis factor alpha (21). Its relatively passive inflammatory nature is convenient, given the high abundance of IgA at mucosal sites, where a continuous exposure to microorganisms and foreign molecules would otherwise cause host cell damage.

After response initiation and coating by active complement complexes on the Fc region, the IgA1 isotype has been reported to be able to detach from the antigenic surface while retaining its binding properties toward new antigens. This phenomenon is termed complement-coated Ab transfer and is believed to be an efficient mechanism for transferring activated complement compounds to nearby antigens without the need to initialize a new response (23).

Coadministration of IgA and IgG has been shown to induce tumor cell killing by polymorphonuclear cells by activating their respective Fc receptors simultaneously (24). On the other hand, IgA’s affinity to bacterial capsular polysaccharides has (paradoxically) been reported to sterically block IgG binding and the following inflammatory functions (25, 26), thus questioning the robustness of the IgA/IgG synergistic effects.

**EFFECTOR RESPONSES AND THEIR ROLE IN MAb TREATMENTS**

Following the detection of a pathogenic surface and initiation of one of the three pathways, there are three main effector functions that contribute to pathogen removal. These functions and their effect on MAb treatments are outlined below.

**MAC and CDC**

As the complement activation amplifies and propagates, the density of C3b increases dramatically, which leads to the binding of C3b to already formed C3 convertases, producing the C5 convertase [C4b2a3b, (C3b)2Bb]. This permits complement activation to enter the terminal phase, where all three pathways converge. C5 convertase cleaves C5 into C5a and C5b. C5a is a potent soluble anaphylatoxin, whereas C5b quickly associates with C6 and C7 components and partitions into a lipid bilayer membrane. Subsequently, C8 binds to the complex, which then induces the binding and polymerization of 10 to 16 C9 components, producing a channel-like structure that penetrates the cellular membrane, known as the membrane attack complex (MAC). Water, electrolytes, and even enzymes can freely pass the channel, which leads to a disruption of cell homeostasis and cell lysis (12).

MAbs engineered to target specific pathogens can direct a complement activation leading to the development of the MAC, thereby lysing the targeted cells by taking advantage of the body’s own defense system. This action forms the basic mechanism of CDC and is believed to play a major role in Ab-based therapy of certain hematological malignancies and solid tumors (27, 28) and a less-defined role in elimination of pathogens, especially bacterial toxins and viruses (7).

**Opsonization**

The large amounts of opsonins, in particular C3b produced from the amplification loop, efficiently coat the surface of the pathogen, tagging it for recognition by neutrophils, NK cells, and monocytes carrying the CRs and C1q receptors. But as opposed to Ab-mediated cell activation through FcRs, CRs do not internalize particles unless they are costimulated by external factors like tumor necrosis factor alpha, colony-stimulating factors, or the complement anaphylotoxins C3a and C5a. Furthermore, CR-mediated phagocytosis does not release inflammatory mediators like reactive oxygen intermediates and arachidonic acid metabolites (29). This may be a reason why CDCC is believed to have limited influence in clinically available immunotherapies (30).

The polysaccharide β-glucan can enhance CR3-dependent cellular cytotoxicity, sometimes referred to as CR3-DCC (31). It is naturally present on cell walls of yeasts and fungi, but its coadministration in MAb therapy targeting surfaces inherently absent of the molecule has been shown to induce cytotoxicity (32). Activation of complement also facilitates the adaptive immune system via the binding of opsonized antigens to CR2 on B cells, which activates specific Ab production and the differentiation of B memory cells. Thus, complement does not only become activated by Abs, but may direct Ab production against C3b-bound surfaces. Clearly C3b is a key molecule in translating complement activation into effector responses (14).

**Inflammatory Responses**

The potent anaphylatoxins C3a and C5a are capable of inducing an inflammatory state by degranulation of mast cells and basophil granulocytes, giving rise to vasodilation and capillary leakage (14). Furthermore, they are strong chemoattractants that guide the migration of circulating neutrophils, monocytes, and macrophages to the site of complement activation, exerting an important role in indirectly facilitating the interaction between opsonins and phagocytes (4). These powerful bioactive
fragments are quickly cleaved by carboxypeptidases to give C5a-desArg and C3a-desArg. C5a-desArg retains up to 10% of the C5a inflammatory properties, while C3a-desArg is devoid of proinflammatory functions (33).

Though not directly responsible for pathogen clearance, the complement anaphylatoxins with their effector cell-activating and chemoattractive properties are important mediators in any cell-mediated immune response, including Ab-mediated FcR activation (i.e., ADCC). An activated complement response thereby has the potential to act synergistically with ADCC, especially by the C5a-dependent upregulation of activating FcγRIII on macrophages (34, 35).

**MANIPULATING AB-MEDIATED COMPLEMENT RESPONSES**

Many of the MAbs already in clinical use do not seem to exploit the full potential of complement. However, since most of the applied Abs are of the IgG1 isotype that has the potential to activate complement, and has been shown to do so in vitro, their clinical efficiency may be improved by providing the proper conditions for a complement response development, as suggested before (31). The substantial amount of experience within CDC and complement initiation should provide approaches to strategically manipulate the complement system to improve the efficacy of immunotherapies, either by improving CDC or by providing synergistic effects between CDC and ADCC. Different approaches can be applied, as briefly outlined below.

**Increasing Complement Response**

Since Ab density is an important parameter for proper complement activation, choosing the right conserved epitope or introducing a cocktail of MAbs with different epitope specificities may not only avoid escape variants of the targeted pathogen but also result in improved complement effector functions in addition to potential effects of neutralizing properties (19, 36). In general, simulating a controlled pool of polyclonal Abs is believed to have several beneficial roles in terms of broader specificity, potency, and robustness and may target groups of infectious agents that are common for specific diseases or exposures (19, 36). The prevalence of infectious diseases is commonly increased in the case of a dysfunctional or immature immune system, and the effector functions expected to accompany Ab therapies are similarly compromised. Immune function assessment and coadministration of complement sources or adjuvants could therefore be necessary to achieve expected drug effects (7).

A central property of the complement system is its fast-acting nature. Due to its efficient amplification, a response rapidly develops and exerts its function. Within a relatively short period, the plasma becomes drained for native complement proteins, and the constant activity of the nonconsumed regulatory proteins ensures down-regulation of the response. Indeed, in the case of rituximab infusions against chronic lymphocytic leukemia (CLL), the least-abundant complement plasma protein, C2, is rapidly consumed and is the limiting factor of rituximab cell-killing efficiency (37). The same group demonstrated that boosting the rituximab-initiated complement response by administering a secondary Ab toward cell-bound C3b and its breakdown products greatly enhanced C3b coating (38). Based on these findings, it was recently shown that the effect of rituximab on five patients with CLL was markedly improved when coadministered with fresh plasma as a source of uncleaved complement proteins (39). It should be noted that CLL is well associated with low levels of complement proteins, especially classical pathway components and properdin. However, since long, repetitive infusions are not uncommon, consumption of complement proteins is likely to occur, resulting in a reduced therapeutic efficiency and increased risk of infectious diseases. Furthermore, most MAb therapies target extravascular spaces, where complement protein levels may be reduced or unevenly distributed compared to plasma. This may explain why many in vitro experiments performed in serum show high complement contributions, whereas in vivo data are less convincing. If target cells are located in extravascular spaces, it is therefore imperative to evaluate the availability of complement proteins and potentially consider coadministration of a complement protein source at the target site (37, 40).

**Reducing Negative Effects from Complement**

The mechanism of action of MAb therapies is likely to be a combination of ADCC, CDC, and CDCC (Fig. 2). However, the exact nature of their interaction, i.e., whether it is synergistic, additive, or antagonistic, remains uncertain (27, 41). Activated complement components would be expected to have positive effects of the recruitment and activation of phagocytes necessary for ADCC, but recent studies with cancer MAb therapies have questioned the positive contributions from complement. In an in vitro study (42), the activation of complement was found to inhibit NK cell-mediated cytotoxicity brought on by ADCC. This inhibition was due to a C3b-dependent interference of the binding of
NK cells to rituximab, thus preventing the activation of NK cells. In the same study, the depletion of C3b components in an in vivo model was able to enhance the ability of rituximab-coated target cells to activate human NK cells and improve the efficacy of the MAb. Yet another study showed that the presence of C5a in the tumor microenvironment could suppress the antitumor CD8+ T-cell-mediated response, which would normally recruit myeloid-derived suppressor cells into tumors and augment T-cell-directed suppressive abilities (43). The same study showed that deficiency of complement in mice was coupled with a hindered tumor growth, a suppression that was comparable to pharmacologically blocking C5a receptors (C5aRs). The inhibition of C5aR signaling was also associated with enhanced CD8+ T cell antitumor response (43). Since CDC depends on late-stage complement development, attempts that block complement activation or deficiency of complement proteins in specific target tissues or in some individuals is likely to reduce ADCC without gaining any effect from CDC. Accordingly, complete blocking of complement may not be a plausible approach in antimicrobial therapies with Abs.

**COMPLEMENT EVASIVE PROPERTIES OF PATHOGENS**

Pathogens generally lack complement regulatory proteins and are susceptible to opsonization and complement attack. However, millions of years of evolution have allowed pathogenic microorganisms to develop sophisticated strategies to dampen or even overcome complement activity (1, 44, 45, 46). Some have successfully employed surface strategies to mask or camouflage antigenic components on their surfaces, while others can express surface proteins to bind to, recruit, or mimic host complement regulators (44). It is not unusual for pathogens to apply several defense strategies, exploiting complement cascades at different stages (47). *Staphylococcus aureus* is an excellent example of a pathogen that can evade several different points of a complement attack by preventing activation, degrading opsonin C3b, and inhibiting C3 convertase, thereby preventing downstream complement effector responses (44). This pathogen also expresses staphylococcal protein A (SpA) with the ability to bind to the Fc fragments of IgGs, thereby reducing the FcR-mediated phagocytosis (48). Other mechanisms include the expression of adhesins by pathogens to anchor to host cell surfaces or to present invasin to mediate uptake into host cells (49).

All surface strategies serve the purpose of avoiding recognition, opsonization, and clearance by host complement response, which lead to the survival of pathogens in an otherwise immunocompetent host (4, 49). Over and above, mutating or new merging pathogenic microorganisms persist to accomplish new ways to counterstrike complement defense, presenting a real challenge for the host and the application for MAb treatments against certain infectious diseases (5).

Persisting malignant cells have the inherent ability to express high levels of endogenous membrane-bound complement regulators, including CD46, decay-accelerating factor, and CD59, which efficiently prevent complement amplification and MAC formation. They can further block complement activation by recruiting fluid-phase complement regulators, contributing to the evasion of complement surveillance that leads to progression in malignant growth (4). However, considering the success of CDC-dependent MAb treatments against malignant cells with upregulated complement regulators, it is plausible to speculate that a well-targeted complement activation may overcome the pathogen’s immune evasive properties.

**CONCLUSIONS AND FUTURE PERSPECTIVE**

The complement system protects the host from pathogenic invaders in a very effective manner. Although defined as a part of the innate immune system, there is a large overlap area shared with the adaptive effector functions. Complement is able to induce inflammation responses that permit the functions of the adaptive system as well as stimulate B-cell-specific Ab production and differentiation of memory B cells. Likewise, target-bound Abs can act as pattern recognition molecules and activate complement. Further, it interacts dynamically with multiple systems, which highlights the complexity of both the biological system and the complement system. The poor understanding of this complexity has led to past failures in the pharmaceutical development in the field. A particular challenge lies in the in vitro/in vivo correlation, in which theory obtained from the linear and often well-controlled experimental environments fails to apply to in vivo performances, where multiple systems are at play. For example, it might be difficult to predict the biological response in tissues where certain effector proteins are dysregulated or in immunocompromised patients.

Our immune system is in constant battle with invading and opportunistic pathogens. A lowering of this guard, for example, in immune-compromised individuals, could
have consequences that might require pharmaceutical interventions. However, the present anti-infectious development is not advancing at the same pace as the rapid emerging strategies of pathogens to counterstrike both the immune system and the current broad-spectrum antibiotic treatments. On the other hand, particulate nanoparticles are receiving increasing attention to enhance the immunogenicity of subunit vaccines through both antigen protection and targeting to antigen-presenting cells as well as immunostimulation (50). The latter may involve the complement system (for instance, some complement activation products can induce B cell activation) or direct activation of the NALP3 inflammasome complex (apoptosis-associated speck-like protein and caspase 1 protease), which in turn cleave and activate the immunostimulatory cytokine interleukin 1β (51).

Ab treatment holds the potential to open a new approach to fight infectious diseases. Properties like direct targeting and selectivity, even for mutant strains, should be taken advantage of. However, issues such as efficiency and precision of diagnosis, cost of drug discovery, and the lack of comprehensive understanding of the mode of action of development candidates signify that much more attention is needed to succeed in building this new platform. When their potentials are fully explored, they would definitely provide a promising future for complement in Ab treatments.

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